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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,238	03/12/2004	Elliott Richelson	07039-126002	7520

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,238	RICHELSON ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 15-26 are presently pending for examination.

Response to Arguments/Amendment

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

5. Instant claim 15 was amended to recite "*a molecule* comprising a polyamide nucleic acid," and further wherein "*said molecule engenders a biological response.*" The scope of the claimed invention now reads beyond the scope of the disclosure as originally filed. As support for this amendment Applicant made reference to page 1, 2nd paragraph of the specification as filed, and Example 5, starting at page 49. Page 1 of the specification does not provide for a generic molecule of undefined chemical composition comprising a PNA oligomer. Example 5 provides support for modified PNA oligomers, comprising various groups useful for detecting the presence of PNA

oligomers in tissue, such as tritiated mono-, di, and tri-methylated PNA, iodinated PNA, and PNA oligomers comprising a fluorescent tag.

There is no support in the passages of the specification referenced by Applicants in their response filed 8-20-07 for a generic molecule comprising a polyamide nucleic. The scope of the term molecule can encompass virtually any form of delivery vehicle, such as a liposome, virus particle, microparticle, nanoparticle and etc. However, Applicant's specification as filed does not provide adequate support for the full scope of the instantly amended claims.

Applicant is required to cancel the new matter in the reply to this Office Action.

6. Claims 15-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the NTRA-PNA oligomer to "engender a biological response" in a rat challenged with neurotensin, and for reducing the expression of a target nucleic acid comprising the delivery of a polyamide nucleic acid oligomer comprising a neutral amide backbone, and comprising a sequence complementary to said target nucleic acid, does not reasonably provide enablement for the amelioration of any and all disease conditions in any mammal comprising the delivery of ***a molecule comprising a polyamide nucleic acid oligomer***, and having a sequence complementary to a target nucleic acid, wherein the overexpression of said target nucleic acid is associated with said disease condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. Applicant's arguments filed 8/20/07 have been fully considered but they are not persuasive. Applicants respectfully disagreed with this rejection but did not provide any arguments addressing the merits of the rejection. Applicants also provided multiple copies of declarations filed during the prosecution of US Patent Application Nos. 09/168,791, 08/953,269, and 09/016,685. The examiner agrees that the multiple Declarations filed under 37 CFR § 1.132 demonstrate the *in vivo* administration of multiple PNA oligomers targeting a variety of mRNA targets, wherein a sequence specific biological response was detected after *in vivo* administration of the PNA oligomer. However, to the extent that the instant claims have been amended to recite the administration of *a molecule comprising a peptide nucleic acid oligomer under conditions wherein the molecule engenders a biological response in a sequence specific manner,* the showing set forth in these declarations is not commensurate in scope with the instantly claimed invention. The instant claims now read on a molecule of undefined composition, and chemical structure, wherein the molecule comprises a PNA oligomer, the term "comprises" as it relates to the molecule is not specifically defined such that the term can be interpreted as meaning wherein the PNA is conjugated to, encapsulated in, dispersed within, or etc., with respect to the molecule. Moreover, the scope of the term "molecule" is so vast that it essentially can encompass anything either known, or yet to be discovered. Therefore, to the extent that Applicant's amendment has significantly changed the breadth of the claimed invention, the Declarations submitted under 37 CFR 1.132 filed 8/20/07 are insufficient to overcome the rejection of claims 15-26 based upon 35 USC § 112, 1st paragraph as set forth in the

last Office action because the showing is not commensurate in scope with the instantly claimed invention.

As stated in the prior Office Action, the cellular uptake of PNA oligomers is variable depending on the modification of PNA, as stated previously concerning antisense compounds. Moreover, Tyler et al. admits in their concluding remarks that "[f]urther experiments must be done in order to gain a fuller understanding of how PNAs are blocking protein expression and what happens to the PNAs within the animal and within the cell." Furthermore, Tyler et al. states that "applicability {of PNAs} to other types of proteins has yet to be examined," this statement suggests that the observations of Tyler et al. were not readily applicable to the delivery of all PNA oligomers for regulating the expression of all target genes.

Koppelhus et al. (2002) et al., page 52, 2nd paragraph, teach: A major obstacle for in vivo and ex vivo studies of the potential of PNA as antisense agent is the limited membrane permeability...and several methods have been applied to overcome the problem of delivery. Among these is the conjugation of PNA to certain "Trojan peptides" reported to have a general cell membrane-penetrating capacity, making them capable of transporting a conjugated cargo to the interior of the cells." Moreover, on page 61, 2nd paragraph, Koppelhus et al. observed that "[O]ur results clearly demonstrate that uptake of PNA can be achieved in most of the tested cell types by conjugation to the peptides. However, the results also show that most of the PNA ends up in vesicular compartments of the cells. Therefore, the internalized PNA is not evenly distributed in the cytoplasm, and it is not significantly present in the nucleus. Thus, the major fraction

of PNA is not present in the cellular compartments where it is supposed to exert its function as antisense agent." However, only a small amount of "the PNA escapes endocytotic entrapment and, thus, is able to act as an antisense agent.....Only carefully performed antisense experiments controlling for a specific effect on gene expression, including proper mismatch or genetic controls, will be able to conclusively demonstrate that this is the case. A comprehensive study being carried out in our laboratory is aimed at answering this question."

According to Rasmussen et al. (2006), several delivery protocols have been devised to overcome the poor cellular uptake of unmodified PNA. In regards to the various published studies of PNA in cellular systems, Rasmussen et al. stated (see page 44, 2nd paragraph): "To date, the published studies of PNA in cellular systems often represent isolated efforts in which a certain delivery protocol has been used in a single cell type during the investigation of a given gene by a specific methodology. The diversity in cell type, application, and methodology in these papers makes it virtually impossible to make reliable assessments about the relative efficiency of the different protocols." Moreover, Rasmussen et al. compared the efficacy of different transfection protocols. The study concluded with the following paragraph (see page 56):

"A final and important lesson from the present study was the finding that because of uncontrollable biologic factors, the absolute optimal transfection conditions will vary from experiment to experiment. Thus, to achieve really optimal cellular delivery of PNA in a specific experiment, these variations should be taken into account. This means that even though an optimized transfection protocol has been established, each experiment should include a systematic variation (around the optimal values) of critical transfection parameters, such as the concentration of PNA or the transfection reagent."

It is noted that the instant specification was filed on 3/12/04, however it claims priority back to 10/17/1997. As per MPEP § 2164.05(a) [R-2] "[W]hether the

specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

In the instant case, the Declaration evidence provided by Applicants do not address the unpredictability associated with significantly low cellular permeability known to be associated with PNA oligomers such that the skilled artisan following the teachings of the specification as filed would have been able to overcome this well known obstacle associated with the use of PNA oligomers *in vivo.* As stated in the prior Office Action, based upon the disclosures of Tyler et al. (1998), Koppelhus et al. (2002) and Rasmussen et al. (2006), it is clear that even today there is a significant level of unpredictability associated with the *in vivo* efficacy of PNA oligomers, particularly in regards to the variation in behavior of the oligomer as it relates to different cell types

and methodology. Therefore, since the state of the art in regards to the use of PNA oligomers in antisense or antigene therapy remains unpredictable (as evidenced by the above references) it is concluded that the skilled artisan would have had to resort to undue experimentation to practice the full scope of the claimed invention due to significant breadth of the claims, the known unpredictability associated with the cellular uptake of PNA oligomers into cells, and the known variability associated with PNA behavior in different cells types, and the limited guidance provided in the specification as filed.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Epps-Ford, Ph.D.
Primary Examiner
Art Unit 1633

JLE